CANCER TREATMENT WITH AN ANTIBODY

[0001] The present invention provides a specific binding molecule for use in the treatment of cancer in a subject. The specific binding molecule binds human annexin-A1 (Anx-A1), and in particular embodiments is an antibody or antibody fragment.

[0002] Cancer is a group of diseases characterised by abnormal cell growth. Characteristically, the abnormal cell growth associated with cancer results in the formation of a tumour (a solid mass of cells formed due to abnormal cell growth), though this is not always the case (particularly in cancers of the blood). In 2010 (the most recent year for which detailed statistics are available), across the world more people (about 8 million) died from cancer than any other single cause (Lozano et al., Lancet 380: 2095-2128, 2012). Furthermore, as populations across the world age, cancer rates are expected to increase. There is thus an urgent need for new and improved therapies for cancer.

[0003] Moreover, many cancer deaths are a result of a cancer becoming resistant to chemotherapy drugs. Methods by which cancers become drug-resistant are reviewed in Housman et al. (*Cancers* 6: 1769-1792, 2014). As detailed therein, cancers may become drug-resistant by a variety of different mechanisms, including inactivation or metabolism of drugs (or the prevention of their metabolic activation), mutation or alteration of drug target and drug efflux via ABC transporters. Such mechanisms can result in cancers becoming multidrug resistant (MDR). As discussed below, drug resistance is a particular problem for therapy with platinum-based chemotherapy agents.

[0004] Platinum-based chemotherapy agents are a common first-line treatment option in several different cancers, including testicular cancer, ovarian cancer, colorectal cancer, cervical cancer, breast cancer, bladder cancer, head and neck cancers, oesophageal cancer, lung cancer, mesothelioma, lymphoma, brain tumours and neuroblastoma. Platinum-based chemotherapy agents include cisplatin, oxaliplatin and carboplatin. All platinum-based chemotherapy agents work in essentially the same way, by reacting with the N-7 position at guanine residues to form inter- and intrastrand DNA crosslinks and DNA-protein crosslinks. The crosslinks inhibit DNA synthesis and/or repair, and cause initiation of apoptosis (Shen et al., *Pharmacol. Rev.* 64: 706-721, 2012). However, while patients generally initially respond well to platinum-based chemotherapy, the large majority then relapse due to the development of resistance to the treatment (particularly in the case of cisplatin), resulting in treatment failure (Shen et al., supra). Thus the development of resistance to platinum-based therapies is a significant challenge in oncology today. Cancers develop resistance to platinum-based therapies via a number of mechanisms, including reduction of accumulation of platinum-based chemotherapy agents in target cells (due to reduced influx and/or increased efflux) and (re-)activation of DNA repair pathways.

[0005] Thus the development of resistance to platinum-based therapies is a significant challenge in oncology today. New treatment options for cancers that are or have become resistant to traditional chemotherapeutics (particularly platinum-based chemotherapeutics) are urgently needed.

[0006] The present inventors have discovered that particular specific binding molecules (e.g. antibodies) against Anx-A1 are effective in treating cancer. The molecules have been found to be particularly effective in treating drug-resistant cancer, including cancer that is resistant to platinum-based chemotherapy. The present invention thus provides a new treatment option for cancer patients, particularly for patients with cancer that is resistant to chemotherapy agents. Such a treatment option answers an urgent need for new therapies for individuals whose disease is unresponsive to traditional chemotherapy.

[0007] The specific binding molecules of the invention have been found to be effective in the treatment of a wide variety of cancers, including breast cancer, colorectal cancer, ovarian cancer, lung cancer and pancreatic cancer.

[0008] Breast cancer is the most common cancer among women, and causes more deaths in women worldwide than any other cancer (Becker, *Int J Gynaecol Obstet* 131 (2015), S36-S39). Over 55,000 cases of breast cancer are diagnosed each year in the UK (and over 300 cases in men). Although the mortality rate for breast cancer is lower than for many other cancers, in the UK over 11,000 deaths annually are caused by breast cancer. Breast cancer lacking expression of the oestrogen receptor, progesterone receptor and the hormone epidermal growth factor receptor HER2 (known as triple negative breast cancer) is particularly difficult to treat, since many modern breast cancer drugs target these receptors. The specific binding molecules of the invention have been found to be effective in treating breast cancer, including triple negative breast cancer, providing an important new treatment option for this disease.

[0009] Ovarian cancer is another cancer common in women, which is difficult to treat. In the UK alone there are over 7,500 incidences of ovarian cancer every year, resulting in over 4,000 deaths (ovarian cancer is frequently diagnosed at a late stage, resulting in this relatively low survival rate). Pancreatic cancer is relatively common, with over 9,000 cases each year in the UK alone, but it is known to be one of the most untreatable cancers, with a survival rate of less than 1% (again, this is primarily due to the disease being diagnosed at a late stage). The specific binding molecules of the invention have been found to be effective in treating both of these cancers, providing a much-needed new therapy for cancers that are hard to treat. Colorectal (or bowel) cancer is also a common cancer with 42,000 cases diagnosed in the UK each year. Despite being only the fourth most common cancer in the UK it is the second most common cancer resulting in death. Similarly, lung cancer is diagnosed in over 47,000 individuals each year in the UK with only 5% surviving for ten years or more after diagnosis. The specific binding molecules of the invention offer useful new therapies for these cancers.

[0010] Full length human Anx-A1 has the amino acid sequence set forth in SEQ ID NO: 17. Anx-A1 is a member of the annexin protein family. Most proteins of this family, including Anx-A1, are characterised by the presence of a "core" region comprising four, homologous, repeating domains, each of which comprises at least one Ca^{2+}-binding site. Each member of the family is distinguished by a unique N-terminal region. Anx-A1 is a monomeric amphipathic protein, predominantly located in the cytoplasm of cells in which it is expressed. However, Anx-A1 can also be exported, resulting in cell surface localisation (D'Acquisto et al., *Br. J. Pharmacol.* 155: 152-169, 2008).

[0011] Anx-A1 is known to play a role in regulation of the immune system, being involved in the homeostasis of various cell types of both the innate and adaptive immune